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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,683	SCHWENK ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19,24,25,28-30,32-41 and 43-58* is/are pending in the application.

4a) Of the above claim(s) *47 and 49-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,24,25,28-30,32-41,43-46,48 and 53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-10-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-10-10 has been entered.

Claims 1-16, 20-23, 26, 27, 31, 42 have been canceled. Claims 17-19, 24, 25, 28-30, 32-41, 43-58 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 8-10-10 have been fully considered but they are not persuasive.

Election/Restrictions

Claims 47 and 49-52 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 1-28-08.

Claims 17-19, 24, 25, 28-30, 32-41, 43-46, 48 and 53-58 are under consideration.

Claim Objections

The abbreviations in claim 33 "CAGGS, hCMV, PGK, FABP, Lck, CamKII, CD19... ...aP2... ...MCK, MyHC, WAP, Col2A, Mx, tet and trex" should be spelled out first and then abbreviated (i.e. human cytomegalovirus (hCMV)).

Claim Rejections - 35 USC § 112

New Matter

Claims 17-19, 24, 25, 28-30, 32-41, 43-46, 48 and 53-56 remain and claims 57 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "Rosa26 locus" as amended has support on pg 8, lines 1-2.

The rejection of claim 17 regarding the phrase "a DNA sequence which can be converted into such gene expression cassette" has been withdrawn in view of pg 4, point to, line 3.

Claim 53 remains new matter. Support cannot be found for expressing a gene of interest and evaluating the function of the gene. Pg 5, lines 9-10, teaches the transgenic can be used for gene function studies but does not teach the steps of expressing a gene of interest and evaluating the function of the gene as claimed. It is not readily apparent applicants contemplated the specific steps claimed. Applicants

argue there is no requirement that what is claimed appear ipsis verbis. Applicants' argument is not persuasive. The phrase is not implicit from the teachings in the specification.

Claim 54 remains new matter. Support cannot be found for "evaluating the effect of the drug candidate on the gene of interest." Pg 5, line 9-10, teaches the transgenic can be used for drug development but does not reasonably imply the steps of contacting a drug candidate with a biological entity and evaluating the effect of the drug as claimed. It is not readily apparent applicants contemplated the specific steps claimed. Applicants argue there is no requirement that what is claimed appear ipsis verbis. Applicants' argument is not persuasive. The phrase is not implicit from the teachings in the specification.

Claim 55 remains new matter. Support cannot be found for providing an animal model of disease, "expression of the gene of interest models a disease state of said animal", contacting a "biological entity" with a drug candidate, and evaluating the effect of the drug on the gene of interest. Pg 5, line 9-10, teaches the transgenic can be used as disease model animals but does not teach using models of disease to test drugs or "expression of a gene of interest models a disease state." It is not readily apparent applicants contemplated the specific steps claimed. Applicants argue there is no requirement that what is claimed appear ipsis verbis. Applicants' argument is not persuasive. The phrase is not implicit from the teachings in the specification.

Claim 56, step b), remains new matter. Pg 9, last three lines, states: "a donor DNA comprising the same two mutually incompatible first RRSs contained in the

acceptor DNA by utilizing a recombination vector as defined above". However, step b) requires "(b) introducing a recombination vector comprising a functional DNA sequence into the acceptor DNA-modified eukaryotic cell, the functional DNA sequence in the recombination vector being donor DNA flanked by two mutually incompatible RRSs that are identical to the two mutually incompatible RRSs in the acceptor DNA". Pg 9 does not contemplate a recombination vector comprising a "functional DNA sequence", that the two RSSs "flank" the donor DNA or that the two RSSs are identical to the RSSs of step a) as claimed. It is not readily apparent applicants contemplated the step now claimed. Applicants point to page 9 and pg 4 which describe "recombinase mediated recombination" but do not specifically imply "(b) introducing a recombination vector comprising a functional DNA sequence into the acceptor DNA-modified eukaryotic cell, the functional DNA sequence in the recombination vector being donor DNA flanked by two mutually incompatible RRSs that are identical to the two mutually incompatible RRSs in the acceptor DNA" as claimed.

Indefiniteness

Claims 17-19, 24, 25, 28-30, 32-46, 53-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 as amended is indefinite because "a modified Rosa26 locus" does not make sense. A locus is a position on a chromosome. While the structure of the gene may be modified, those of skill would not modify the position of Rosa26. "Wherein said promoter is heterologous to the Rosa26 locus" does not make sense either because a

promoter may be heterologous to other DNA sequences but not to a position on a chromosome.

The metes and bounds of what applicants consider an "inducible ubiquitous promoter" and "inducible tissue specific promoter" in claim 32 remain indefinite. The structure of such promoters is not defined in the specification or the art at the time of filing. Applicants argue those of skill would know what the phrase meant. Applicants' argument is not persuasive. While the specification need not define the phrase, those of skill would have to look to the art at the time of filing to determine the meaning; however, the art at the time of filing did not define which promoters are "inducible ubiquitous promoters" and "inducible tissue specific promoters". Without a definition, those of skill would not know when they were infringing on the claim. Applicants point to Kuhn, who taught inducible promoters, and the list of promoters on pg 8, which generically lists numerous promoters. Applicants' arguments are not persuasive. While the Mx1 promoter may be inducible, it is not readily apparent that the Mx1 promoter is "an inducible ubiquitous" promoter as claimed. Nor does the list on pg 8 of the specification define which promoters are "inducible ubiquitous" or "inducible tissue specific" as claimed.

The rejection regarding the metes and bounds of what applicants consider a "CAGGS, hCMV, PGK, FABP, Lck, CamKII, CD19... ...aP2... ...MCK, MyHC, WAP, Col2A, Mx, tet and trex" promoter in claim 33 has been withdrawn in view of applicants' arguments. The abbreviations should be spelled out first and then abbreviated (see claim objection above).

Claim 45 remains indefinite because it is unclear what applicants consider an "inactive" positive selection marker. Applicants point to Fukushige who taught a "positive-selection lox integration vector". Applicants' argument is not persuasive. It is unclear what applicants or Fukushige consider an "inactive positive selection marker.

Claim 55 remains indefinite because it is unclear how an animal comprising a cell made by the method of claim 17 is a model of an animal disease. The claim encompasses an animal having one cell made by the method of claim 17, which cannot be a model of disease. Accordingly, there is no nexus between an animal with a cell made by claim 17 as broadly claimed and "models of disease." Applicants argue the animal models disease because "expression of the gene of interest models a disease state in said animal model." Applicants' argument is not persuasive. Expression of a gene does not necessarily model a disease state. Expression of Neomycin does not model a disease state. Low level expression of insulin does not model a disease state. What is required is a non-human animal having a phenotype of a disease state.

Claim 56 remains indefinite because the metes and bounds of what applicants consider "two mutually incompatible RRSs" does not clearly set forth the structure or function of the acceptor DNA. Pg 9 uses the phrase (last 5 lines) and pg 10, first four lines, use the term RSS, but the metes and bounds the phrase are unclear. Using the phrase does not mean the phrase is defined. Applicants have not disclosed the structure or function of "two mutually incompatible RRSs" on pg 9, 10 or any where else in the specification. Without such guidance, those of skill would not know when they were infringing on the claim. Claims 43-45 are included because they are dependent

upon claim 56. Applicants point to Schlake. Applicants' argument is not persuasive. Schlake has not been provided. It is not readily apparent Schlake uses the phrase or defines the phrase.

Claim Rejections - 35 USC § 102

Claims 17-25, 28-30, 32-32, 34-38, 43-46, 48 and 53-56 remain rejected under 35 U.S.C. 102(b) as being anticipated by Soprano (WO99/53017) for reasons of record.

Soriano made a Rosa26 transgenic mouse by introducing a DNA cassette comprising a LacZ gene flanked by loxP sites into the Rosa26 gene of a mouse ES cell and implanting the ES cell into a mouse blastocyst. The LacZ gene was under the control of the mouse Rosa26 promoter (Example 1, pg 30) and is considered a "selectable marker" gene as newly amended. Soriano also taught making a Rosa26Cre transgenic mouse (Example 2, pg 41) by introducing a construct into ES cells, the construct comprising a deletor cassette comprising a recombinase gene operably linked to an upstream splice acceptor (SA and a downstream polyA sequence with a positive selection cassette comprising a PGK promoter, the neo gene and a polyadenylation sequence (pg 7, lines 2-10). The construct was inserted into the targeting vector comprising homology arms for the Rosa26 gene and a diphtheria toxin gene for negative selection (pg 7, line 9-10; pg 7, line 1-2). Soriano also made a transgenic mouse by introducing a targeting vector into mouse ES cells, the vector comprising a reporter cassette comprising a splice acceptor operably linked to stuffer DNA flanked by two loxP sites (pg 7, lines 10-16); the stuffer DNA comprised a PGK promoter, the neo gene and four polyA sites (pg 44, Example 3). The coding sequence described by

Soriano is a "DNA sequence which can be converted into such gene expression cassette."

The cassette comprises a gene of interest operably linked to a PGK promoter (Fig. 1C; Fig. 4), which is "heterologous to the Rosa26 locus" as claimed. In the alternative, Soriano taught numerous Rosa26 promoter fragments including mutagenized promoters, (pg 34-35) which are "heterologous" as claimed because they are different in structure (especially the mutagenized Rosa26 promoter) than the original Rosa26 promoter (Heterologous is defined as "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010)). In a third alternative, Soriano taught "isogenic homology regions flank the exogenous targeting construct sequence that is to replace the targeted promoter gene locus sequence" (pg 26, lines 1-3, emphasis added), i.e. to replace the Rosa26 promoter with a heterologous promoter via recombination, which is equivalent to a promoter that is "heterologous to the Rosa26 gene" as claimed.

It is noted that "heterologous" means being from another tissue (Dorland Medical Dictionary definition of "heterologous", 2010) or "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010). "Heterologous" is not limited to "xenogeneic" (which means from another species).

The Rosa26 promoter fragments included mutagenized promoters, (pg 34-35) which they have a different structure than the original Rosa26 promoter. Heterologous

is defined as "differing in structure and origin: describes organisms or parts that differ from each other in structure or origin" (Encarta Dictionary definition of "heterologous", 2010).

The cassette comprises a gene of interest operably linked to a PGK promoter (Fig. 1C; Fig. 4), which is "heterologous to the Rosa26 locus" as claimed. Soriano also taught "isogenic homology regions flank the exogenous targeting construct sequence that is to replace the targeted promoter gene locus sequence" (pg 26, lines 1-3), i.e. to replace the Rosa26 promoter with a heterologous promoter using recombination, which is equivalent to a promoter that is "heterologous to the Rosa26 locus" as claimed.

Applicants argue Soriano did not teach a selectable marker gene as newly claimed. Applicants' argument is not persuasive. The LacZ gene was under the control of the mouse Rosa26 promoter (Example 1, pg 30) and is considered a "selectable marker" gene as newly amended.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday through Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Primary Patent Examiner